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1    **The laboratory of clinical virology in monitoring the patients undergoing**  
2    **monoclonal antibody therapy**

3

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18

19    **Abstract**

20    The relevant efficacy of monoclonal antibodies (mAbs) has resulted in the successful  
21    treatment of several diseases, although susceptibility to infections remains a major  
22    problem. This review summarizes aspects of the literature regarding viral infections and  
23    mAbs, specifically addressing the risk of infection/reactivation, the measures that can  
24    reduce this risk, and the role played by the laboratory of clinical virology in monitoring the  
25    patients undergoing mAb therapy.

26

27    **Keywords**

28    Monoclonal antibodies; herpesviruses; polyomaviruses; hepatitis viruses; monitoring.

29

## 30    **Introduction**

31    The treatment of several medical conditions, such as cancer and autoimmune diseases,  
32    has been revolutionized following the introduction of biologic therapies targeting specific  
33    components of pathways involved in the pathogenic mechanisms. These agents are  
34    prevalently monoclonal antibodies (mAbs). Immunotherapy developed with the discovery  
35    of antibodies structure and the introduction of hybridoma technology, which provided the  
36    first source of mAbs [1]. Initially, murine mAbs (suffix *-omab*) were burdened by major  
37    problems due to immune complex formation and inadequate recruitment of host effector  
38    functions. To overcome this, murine molecules were engineered to remove immunogenic  
39    content and to increase the immunomodulant efficiency; this was achieved by the  
40    production of chimeric (composed of murine variable regions fused onto human constant  
41    regions, ~65% human component; suffix *-ximab*) and humanized (produced by grafting  
42    murine hypervariable aminoacid domain into human antibodies, ~95% human component;  
43    suffix *-zumab*) antibodies. Extensive researches are currently conducted to originate  
44    mAbs for several diseases, such as rheumatoid arthritis, multiple sclerosis, inflammatory  
45    bowel diseases, and many types of neoplasms. However, susceptibility to infections  
46    remains a major concern, as the target of these mAbs are molecules or cells involved in  
47    immune anti-infectious pathways. The severity of these infections can be influenced by the  
48    protocol utilized (dosage, frequency, and route of administration). Considering the most  
49    used mAbs in clinical practice, the reported infectious complications remain low and limit  
50    particularly the utilization of mAbs targeting antigens such as CD52, CD20, tumor necrosis  
51    factor (TNF)- $\alpha$  and the integrin very late antigen (VLA)-4 [2]. Beside bacterial and fungal  
52    infections, viral infections/reactivations represent important factors limiting the utilization of  
53    biological agents (Table 1).

**55 Anti-CD52: alemtuzumab**

56 Alemtuzumab is a humanized anti-CD52 antibody (Campath®), that is mainly expressed  
57 on the surface of peripheral B- and T-cells, both normal and malignant, monocytes,  
58 thymocytes, natural killer cells and macrophages, whereas it is not expressed on  
59 erythrocytes or platelets. This mechanism of action makes alemtuzumab indicated for the  
60 treatment of chronic lymphocytic leukemia, non-Hodgkin lymphomas, post-transplantation  
61 and graft-versus-host disease. Treatment results in lymphoid ablation. In this context,  
62 reactivation of cytomegalovirus (CMV) is an important problem, having been reported in 6-  
63 66% of patients [3]. The wide range of reported incidence might be a result of differences  
64 in study design, population, and viral detection modes; moreover, earlier studies might  
65 have underreported the incidence of CMV reactivation, because CMV was not routinely  
66 monitored. Nevertheless, the benefit/risk ratio favors its utilization associated to a close  
67 virological monitoring for early detection of reactivation, as pre-emptive treatment prevents  
68 the occurrence of potentially life-threatening disease and the initiation of anti-CMV  
69 treatment avoids the interruption of alemtuzumab. Cytomegalovirus reactivation is typically  
70 observed between 4 and 6 weeks after the initiation of treatment [4]. Usually, given the  
71 high background of CMV-seropositivity, reactivation is monitored weekly by a sensitive  
72 detection method (CMV-DNAemia). In clinical trials, among the exclusion criteria for the  
73 recruitment, CMV-DNAemia positivity at screening makes the patient not eligible.  
74 Treatment to reduce viral load to a non-detectable level is required and study entry is  
75 possible once the infection has been treated. Among exclusion criteria, there are active or  
76 prior viral hepatitis B or C or positivity for hepatitis B serology. Patients with hepatitis B  
77 surface antibodies (HBsAb) with documented history of prior hepatitis B immunization are

78 eligible if other criteria are met (i.e. negativity for HBsAg, HBcAb, and anti-HCV). Patients  
79 with HIV-infection are excluded. In Figure 1, an algorithm for the evaluation of viral  
80 infections in relation to the administration of alemtuzumab is reported.

81

## 82 **Anti-CD20: rituximab**

83 Rituximab (Mabthera® or Rituxan®) is a chimeric mAb targeting the CD20 molecule, that  
84 is expressed on the normal B-cell lineage (from pre-B stage to memory stage) as well as  
85 on abnormal B-lymphocytes. Rituximab has been approved for the treatment of indolent  
86 CD20, B-cell non-Hodgkin lymphomas, and chronic lymphocytic leukemia, as well as for  
87 that of moderate-to-severe rheumatoid arthritis. Several viral infections related to rituximab  
88 have been reported. In a metanalysis [5], 64 cases of serious viral infection after rituximab  
89 treatment were found, in particular HBV reactivation in patients with chronic lymphocytic  
90 leukemia and lymphomas [5,6-9], followed by CMV, varicella-zoster virus, and others. A  
91 close monitoring for viral infections, particularly HBV and CMV, by molecular methods is  
92 recommended. Periodic monitoring of HBV-DNA may predict HBV reactivation, thus being  
93 advantageous in terms of costs; it is also essential in cases with HBV-DNA mutations and  
94 when antibody expression is weak. The identification of HBV reactivation at an early stage  
95 is important; therefore, in addition to HBV-DNA monitoring, it should be recommended to  
96 evaluate changes in anti-HB titers [10]. Viral reactivation of polyomavirus JC from sites of  
97 latency leading to the development of infection and destruction of the oligodendrocytes is  
98 the pathogenic mechanism responsible for progressive multifocal leukoencephalopathy  
99 (PML). To date, 57 PML cases have occurred in patients treated with rituximab [11,12]. A  
100 high degree of awareness for PML facilitates case identification; as a definitive diagnosis  
101 of PML is based on clinical, neuroimaging, histopathologic findings, as well as on the

102 detection of JCV in the brain tissue, less invasive methods based on the detection of JCV-  
103 DNA in cerebrospinal fluid have been proposed. Evaluation of JCV-DNA on serum  
104 specimens seems to display low operating characteristics, given the rarity of PML and the  
105 high incidence of transient viremia (up to 18% in HIV-patients without PML)[13].

106

## 107 **Tumor necrosis factor- $\alpha$ antagonists**

108 Monoclonal antibodies that antagonize TNF- $\alpha$  (i.e. infliximab, etanercept, adalimumab,  
109 certolizumab pegol) are used for several inflammatory diseases, such as Crohn's disease,  
110 rheumatoid polyarthritis, psoriasis, ankylosing spondylitis, and juvenile idiopathic arthritis.  
111 While the association with an increased risk of severe bacterial infections and reactivation  
112 of tuberculosis has been recognized, the impact on viral infections is less known. Long-  
113 term safety and efficacy in patients with chronic HBV or HCV and/or HIV infection are  
114 poorly known. However, history or current active HBV, history of HCV and HIV infection  
115 are exclusion criteria for enrollment in clinical trials. As regards HCV, elevated levels of  
116 TNF- $\alpha$  are associated with chronic infection and there is a growing evidence that the  
117 pathogenesis of hepatocyte destruction may be mediated by the upregulation of  
118 inflammatory cytokines such as TNF- $\alpha$ . Therefore, TNF- $\alpha$  antagonists may be beneficial  
119 when used in cases of HCV [14,15] and there are some reports indicating that anti-TNF- $\alpha$   
120 therapy in the setting of HCV appears to be safe. However, as the role of TNF- $\alpha$  is  
121 complex, the FDA points out the possible risk of reactivation of chronic viral hepatitis.  
122 Overall, data on safety and efficacy are conflicting; therefore, the presence of HCV should  
123 not be an absolute contraindication, given an appropriate pretreatment screening and a  
124 close monitoring. For selected patients, anti-TNF- $\alpha$  therapy in the setting of HCV appears  
125 to be safe without apparent influence on the underlying infection. Interval monitoring of



126 serum aminotransferases and HCV viral load is recommended. Elevated levels of TNF- $\alpha$   
127 are also seen in patients with chronic HBV and, in these patients, it may play a role in  
128 clearing and controlling replication by synergizing with interferon; inhibition of TNF- $\alpha$  could  
129 theoretically lead to enhanced viral replication [16,17]. Reports of patients with chronic  
130 HBV who were treated with infliximab or etanercept, and developed a severe reactivation,  
131 sometimes with fulminant hepatitis, have been published [18-21]. In most cases, patients  
132 had chronic HBV with HBsAg positivity, but in others fulminant hepatitis was associated  
133 with a previously unrecognized HBsAg-carrier condition. For HBsAg-negative patients with  
134 a known history of HBV, the risk of reactivation is very low, but it cannot be totally  
135 excluded. Patients who are persistently HBsAg-negative, but have an occult HBV infection,  
136 have also been described. These patients may be at risk of developing a flare of hepatitis  
137 during the course of anti-TNF- $\alpha$  agents as this may interrupt the suppression of viral  
138 replication and gene expression typical for the occult HBV [17]. Evaluation of risk-benefit  
139 profile for specific antiviral treatment with lamivudine should be performed [17]. In  
140 conclusion, screening for HBV in all patients prior to treatment with anti-TNF- $\alpha$  agents  
141 should be recommended and, if treatment has been initiated, carriers of HBV should be  
142 closely monitored for laboratory and clinical signs of viral reactivation during therapy and  
143 for several months following its termination.

144 Few data on the risk of reactivation of herpesvirus infections are available. Several cases  
145 of CMV infection have been reported, although severe clinical manifestations are rare.  
146 Authors suggested the assessment of CMV pp65-antigen levels or quantification of CMV-  
147 DNA in symptomatic patients [22-26]. Limited informations are available on Epstein-Barr  
148 virus reactivation, as well as JCV. Large studies with long follow-up are needed to define  
149 the risk and opportunity for viral monitoring. Epstein-Barr virus is associated with

150 lymphoproliferative diseases in immunosuppressed patients and infliximab treatment has  
151 been resulted in transient elevations in viral load in some patients, although at levels lower  
152 than those associated to lymphoproliferative disorders [27]. Similarly, also limited data are  
153 available on varicella zoster virus and screening recommendations for the presence of  
154 antibodies prior to treatment or a prophylactic vaccination in non-immune patients remain  
155 questionable [28].

156 Specific effects of anti-TNF- $\alpha$  therapy on human papillomavirus-associated diseases  
157 remain unknown, with very few reports suggesting a significantly increased risk in patients  
158 with inflammatory bowel diseases treated with infliximab [29].

159 HIV is considered among the relative contraindications for anti-TNF- $\alpha$  therapy, however its  
160 safety in HIV-infected patients is unknown. Their use should be reserved for highly  
161 selected patients, although further studies are needed. The potential impact of the loss of  
162 HIV control needs to be determined before establishing a clear recommendation; to  
163 promptly identify reactivation of HIV, close monitoring of clinical and laboratory parameters  
164 in these patients is mandatory [17,30].

165 Overall, although several guidelines regarding viral infections monitoring in  
166 immunocompromised patients are available, few address biological therapy. The  
167 appropriate serological tests are poorly defined, although evaluation of HBV status is  
168 widely supported, while HCV and HIV testing seems to be justified in high-risk patients.  
169 The European Crohn's and Colitis Organisation consensus statement recommends  
170 universal testing (HBsAg, anti-HBs, anti-HBc) and HBV vaccination in all the patients with  
171 inflammatory bowel diseases, while no recommendations have been defined for HCV [31].  
172 On the contrary, a consensus statement on pre-treatment testing in rheumatology patients

173 recommends the screening for HBV and HCV in all the patients, without a defined  
174 serological strategy [32].

175

## 176 **Anti-integrin VLA-4**

177 Natalizumab (Tysabri®) is a selective adhesion molecule inhibitor the target of which is  
178 the  $\alpha 4$  subunit of VLA-4 receptor. Natalizumab binds to  $\alpha 4$ -integrin expressed on the  
179 surface of activated T cells and other mononuclear leukocytes, where it prevents adhesion  
180 between the endothelial cell and the immune cell. This action inhibits the migration of  
181 leukocytes into the central nervous system. The main indication for natalizumab treatment  
182 is relapsing-remittent highly inflammatory multiple sclerosis (MS). However, the same  
183 mechanism of action implies a decreased local immune surveillance, thus possibly  
184 contributing to an increased risk of PML,  
185 a demyelinating disease caused by lytic replication of JCV in oligodendrocytes, that is  
186 observed in the setting of profound cellular immunosuppression, such as HIV patients and  
187 individuals exposed to potent antilymphocyte drugs, such as natalizumab, and other  
188 mAbs, such as rituximab and efalizumab.

189 More than 30 PML cases have been reported worldwide in patients receiving natalizumab  
190 monotherapy for MS and data suggests that PML incidence increases with the number of  
191 infusions (increased risk after two years of therapy). Currently, ~30,000 patients treated or  
192 on treatment with natalizumab are being monitored for PML [12].

193

## 194 **Conclusions**

195 The elevated efficacy of mAbs is counterbalanced by an increased risk of infectious  
196 complications. The complete spectrum of viral diseases complicating their administration is  
197 still poorly known, although data are accumulating. Similarly, also virological screening and  
198 monitoring that should be performed in these patients are still undefined and vary largely  
199 depending on underlying disease, type of patients, and protocol. Particular attention is  
200 required for the monitoring of herpesviruses, JCV, HBV and HCV, and data that are being  
201 obtained could represent the basis to define consensus guidelines that take into account  
202 the evaluation of viral status pre-treatment, as well as viral replication/reactivation during  
203 therapy and following its interruption. The possible role played by the specific cellular  
204 immune response in containing viral replication remains to be determined and it is likely  
205 that viro-immunological monitoring could contribute to better understand the immunological  
206 background underlying the occurrence of viral complications and to improve their clinical  
207 management. Overall, the role played by the virology laboratory is relevant as the basal  
208 evaluation of viral infection and the subsequent monitoring in patients treated with  
209 biological agents could allow to start or continue a successful therapy in cases for which  
210 there are few treatment options. As the benefits of these agents outweigh their risks, the  
211 formulation of specific recommendations could allow to identify a small group of patients in  
212 which the treatment cannot be used or must be interrupted. The aim of developing specific  
213 recommendations and guidelines is becoming all the most important considering the  
214 growing utilization of these agents in different clinical contexts.

215

216

217 **Conflict of interests.** None.

## 218   **References**

- 219   1. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined  
220   specificity. *Nature* 1975; 256: 495-497.
- 221   2. Rigal E, Gateault P, Lebranchu Y, Hoarau C. Les complications infectieuses liées à  
222   l'utilisation des anticorps monoclonaux chez home. *Med Sci (Paris)* 2009; 25: 1135-1140.
- 223   3. Cheung WW, Tse E, Leung AYH, Yuen K-Y, Kwong Y-L. Regular virologic surveillance  
224   showed very frequent cytomegalovirus reactivation in patients treated with alemtuzumab.  
225   *Am J Hematol* 2007; 82: 108-111.
- 226   4. O'Brien SM, Keating MJ; Mocarski ES. Updated guidelines on the management of  
227   cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with  
228   alemtuzumab. *Clin Lymphoma Myeloma* 2006; 7: 125-130.
- 229   5. Aksoy S, Harputluoglu H, Kilickap S *et al.* Rituximab-related viral infections in lymphoma  
230   patients. *Leuk Lymphoma* 2007; 48: 1307-1312.
- 231   6. Dervite I, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B  
232   surface antigen who was receiving rituximab. *N Engl J Med* 2001; 344: 68-69.
- 233   7. Tsutsumi Y, Kawamura T, Saitoh S *et al.* Hepatitis B virus reactivation in a case of non-  
234   Hodgkin's lymphoma treated with chemotherapy and rituximab: necessity of prophylaxis  
235   for hepatitis B virus reactivation in rituximab therapy. *Leuk Lymphoma* 2004; 45: 627-629.
- 236   8. Niscola P, Del Principe MI, Maurillo L *et al.* Fulminant B hepatitis in a surface antigen-  
237   negative patient with B-cell chronic lymphocytic leukaemia after rituximab therapy.  
238   *Leukemia* 2005; 19: 1840-1841.

- 239 9. Perceau G, Diris N, Estines O, Derancourt C, Lévy S, Bernard P. Late lethal hepatitis B  
240 virus reactivation after rituximab treatment of low-grade cutaneous B-cell lymphoma. *Br J*  
241 *Dermatol* 2006; 155: 1053-1056.
- 242 10. Tsutsumi Y, Ogasawara R, Kamihara Y *et al.* Rituximab administration and reactivation  
243 of HBV. *Hepat Res Treat* 2010; 2010: 182067.
- 244 11. Carson KR, Evens AM, Richey EA *et al.* Progressive multifocal leukoencephalopathy  
245 after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on  
246 Adverse Drug Events and Reports project. *Blood* 2009; 113: 4834-4840.
- 247 12. Major EO. Progressive multifocal leukoencephalopathy in patients on  
248 immunomodulatory therapies. *Annu Rev Med* 2010; 61: 35-47.
- 249 13. Dubois V, Moret H, Lafon ME *et al.* Prevalence of JC virus viremia in HIV-infected  
250 patients with or without neurological disorders: a prospective study. *J Neurovirol* 1998; 4:  
251 539-544.
- 252 14. Zylberg H, Rimaniol AC, Pol S, *et al.* Soluble tumor necrosis factor receptors in chronic  
253 hepatitis C: a correlation with histological fibrosis and activity. *J Hepatol* 1999; 30: 185-  
254 191.
- 255 15. Zein NN. Etanercept as an adjuvant to interferon and ribavirin in treatment-naïve  
256 patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind,  
257 placebo-controlled study. *J Hepatol* 2005; 42: 315-322.
- 258 16. Herbein G, O'Brien WA. Tumor necrosis factor (TNF)-alpha and TNF receptors in viral  
259 pathogenesis. *Proc Soc Exp Biol Med* 2000; 223: 241-257.

- 260 17. Domm S, Cinatl J, Mrowitz U. The impact of treatment with tumour necrosis factor- $\alpha$   
261 antagonists on the course of chronic viral infections: a review of the literature. *Br J*  
262 *Dermatol* 2008; 159: 1217-1228.
- 263 18. Ostuni P, Botsions C, Punzi L *et al.* Hepatitis B reactivation in a chronic hepatitis B  
264 surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose  
265 methotrexate. *Ann Rheum Dis* 2003; 62: 686-687.
- 266 19. Michel M, Duvoux C, Hezode C *et al.* Fulminant epatiti after inflizimab in a patient with  
267 epatiti B virus treated fora n adult onset Still's disease. *J Rheumatol* 2003; 30: 1624-1625.
- 268 20. Millonig G, Kern M, Ludwiczek O *et al.* Subfulminant epatiti B after infliximab in Crohn's  
269 disease: need for HBV-screening? *World J Gastroenterol* 2006; 12: 974-976.
- 270 21. Montiel PM, Solis JA, Chirinos JA *et al.* Hepatitis B virus reactivation during therapy  
271 with etarecept in an HBsAg-negative and anti-HBs-positive patient. *Liver Int* 2008; 28: 718-  
272 720.
- 273 22. Helbling D, Breitbach TH, Krause M. Disseminated cytomegalovirus infection in  
274 Crohn's disease following anti-tumour necrosis factor therapy. *Eur J Gastroenterol Hepatol*  
275 2002; 14: 1393-1395.
- 276 23. Haerter G, Manfras BJ, Jong-Hesse Y *et al.* Cytomegalovirus retinitis in a patient  
277 treated with anti-tumor necrosis factor alpha antibody therapy for rheumatoid arthritis. *Clin*  
278 *Infect Dis* 2004; 39: e88-94.
- 279 24. Sari I, Birlik M, Gonen C *et al.* Cytomegalovirus colitis in a patient with Behçet's  
280 disease receiving tumor necrosis factor alpha inhibitory treatment. *World J Gastroenterol*  
281 2008; 14: 2912-2914.

- 282 25. Mizuta M, Schuster MG. Cytomegalovirus hepatitis associated with use of anti-tumor  
283 necrosis factor-alpha antibody. *Clin Infect Dis* 2005; 40: 1071-1072.
- 284 26. Kohara MM, Blum RN. Cytomegalovirus ileitis and hemophagocytic syndrome  
285 associated with use of anti-tumor necrosis factor-alpha antibody. *Clin Infect Dis* 2006; 42:  
286 733-734.
- 287 27. Leung VS, Nguyen MT, Bush TM. Disseminated primary varicella after initiation of  
288 infliximab for Crohn's disease. *Am J Gastroenterol* 2004; 99: 2503-2504.
- 289 28. Reijasse D, Le Pendeven C, Cosnes J, et al. Epstein-Barr virus load in Crohn's  
290 diseases: effect of immunosuppressive therapy. *Inflamm Bowel Dis* 2004; 10: 85-90.
- 291 29. Shale MJ, Seow CH, Coffin CS, Kaplan GG, Panaccione R, Ghosh S. Review article:  
292 chronic viral infection in the anti-tumour necrosis factor therapy era in inflammatory bowel  
293 disease. *Aliment Pharmacol Ther* 2010; 31: 20-34.
- 294 30. Cepeda EJ, Williams FM, Ishimori MI et al. The use of anti-tumour necrosis factor  
295 therapy in HIV-positive individuals with rheumatic disease. *Ann Rheum Dis* 2008; 67: 710-  
296 712.
- 297 31. Rahier JF, Ben-Horin S, Chowers Y et al. European evidence-based consensus on the  
298 prevention, diagnosis and management of opportunistic infections in inflammatory bowel  
299 disease. *J Crohn's Colitis* 2009; 3: 47-91.
- 300 32. Furst DE, Keystone EC, Kirkham B et al. Updated consensus statement on biological  
301 agents for the treatment of rheumatic diseases, 2008. *Ann Rheum Dis* 2008; 67: iii2-25.



302 33. Carpenter B, Haque T, Dimopoulou M *et al.* Incidence and dynamics of Epstein-Barr  
303 reactivation after alemtuzumab-based conditioning for allogeneic hematopoietic stem-cell  
304 transplantation. *Transplantation* 2010; 90: 564-570.

305

306 Table 1. Main viral infections/reactivations in patients undergoing monoclonal antibodies  
 307 therapy and monitoring or recommendations. PTLT, post-transplantation  
 308 lymphoproliferative disorders.

	Anti-CD52 (alemtuzumab)	Anti-CD20 (rituximab)	TNF- $\alpha$ antagonists (infliximab, etanercept, adalimumab, certolizumab pegol)	Anti-integrin VLA-4 (natalizumab)
CMV	6-66% reactivation within 4-6 weeks, close monitoring (3,4)	Few cases, close monitoring (5)	Poorly known (22-26)	
HBV	Active and prior infection as exclusion criteria in clinical trials	20-55%, close monitoring (5,6-10)	Case reports, close monitoring, exclusion criteria in clinical trials, but consider occult infection (18- 21)	
HCV	Active and prior infection as exclusion criteria in clinical trials		Poorly known, close monitoring (14,15)	
VZV		Few cases (5)	Poorly known (28)	
JCV		57 cases (11,12)		30 cases (12)
EBV	Up to 40% reactivation, <1% risk PTLD (33)		Poorly known (27)	
HPV			Poorly known (29)	

309

310

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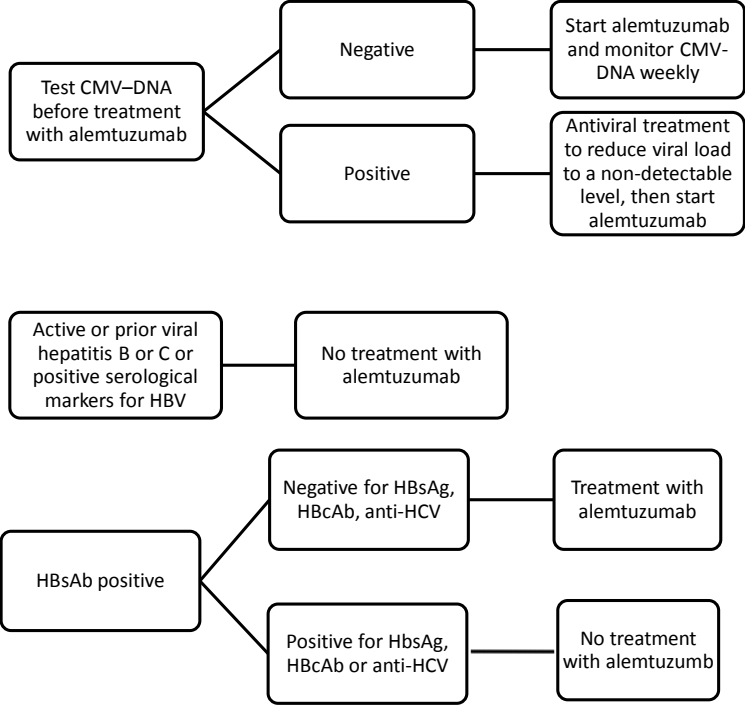
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316 Figure 1. Algorithm for the evaluation of viral infections in relation to the administration of  
317 alemtuzumab.



318